SYNOPSIS

The work reported in the thesis entitled "Studies on drug potentials of some nitrogen and sulfur containing heterocyclic compounds" has been described under the following different six chapters.

CHAPTER – I

[A] INTRODUCTION AND REVIEW OF LITERATURE

[B] PLAN OF WORK

Research on new substances possessing antibacterial activity has attracted considerable attention owing to the continuous increase in bacterial resistance[1]. Further, infection caused by various micro-organisms pose a serious challenge to the medicinal community and need for an effective therapy has led to the search for novel antibacterial agents[2].

The entire research work is on the synthesis, antimicrobial and anti-HIV studies of nitrogen and sulfur containing heterocyclic compounds. All the compounds were designed and synthesized by condensing various pharmacophores and evaluated for their *in vitro* antimicrobial screening against a panel of microorganisms which has shown very promising results.

The thiohydantoin nucleus is a 5-membred ring system containing a reactive cyclic thiourea core. This heterocycle is present in a wide range of biologically active compounds including antiarrhythmic[3], anticonvulsant[4] and antitumor[5] agents. 2-Thiohydantoin[6,7] moiety possesses antiviral, antibacterial, antifungal, herbicidal, anticonvulsant, anti-inflammatory, antiulcer, antiarrhythmic and anti-diabetic, properties. A series of 2-thiohydantoins carrying various heterocyclic substituents such as 5-bromothienylidene, 5-(2-carboxyphenylthio) thienylidene & 4H-thieno-[2,3-b][1] benzothiopyran-4-one have been synthesized and tested for their activity HIV-1 virus and as antitumor agents[8].

Styryl derivatives are known to posses their antimicrobial activities[9].

4-Thiozolidinone and its derivatives are known to possess a variety of physiological properties viz, analgesic, local[10] and spiral[11] anaesthetic, CNS

stimulant[12], hypnotics[13], antibacterial[14], antifungal[15], antitubercular[16], anticancer and anti-HIV[17].

The quinazoline ring skeleton is widely found in alkaloids and many biologically active compounds[18]. Quinazolinone a nitrogenious heterocycles, have attracted a great deal of interest because of such unique biological activities as anticancer[19], antiproliferative agents[20], anti-inflammatory[21], anticonvulsant, CNS depressant and anti-HIV agents[22].

Quinazolin-4(3*H*)-ones having substitution at position-3 with substituted phenyl ring s[23,24], bridged phenyl rings[25,26], heterocyclic rings[27] and aliphatic systems[28,29] have been reported to be associated with antimicrobial properties[30].

Thiourea derivatives of aryl ethyl amine are used in the synthesis of anti-HIV[31], antitumor[32], antibacterial[33] and antifungal[34] agents. Thiourea derivatives are more potent than the other anti-viral drugs against multidrug resistance HIV-1 strain RT-MDR with a V106-A mutation[35,36].

Urea derivatives are reported to possess antibacterial[37], antimicrobial, antifungal, anticancer[38] and anticonvulsant activities[39].

Semicarbazide and its derivatives are reported to be physiologically and pharmacologically active and find applications in the treatment of several diseases[40].

On the other hand semicarbazides are an important class of molecules with a large spectrum of biological properties. These compounds have been studied as anticonvulsant, antitubercular[41] & antinociceptive[42] agents. Aryl semicarbazides are reported to display excellent anti-convulsant[43] activity in mice and rats compared to that of phenytoin.

Semicarbazone, themselves are of much interest due to a wide spectrum of pharmacological activities like antibacterial, antifungal[44], anticonvulsant[45], antitubercular[46], analgesic and anti-inflammatory[47] etc.

Semicarbazones have been recognized as a promising pharmacophore and a number of semicarbazone derivatives have been synthesized and tested for their anticonvulsant activity[48-50].

Thiosemicarbazides are valuable building blocks for the synthesis of five-membered heterocycles[51].

Thiosemicarbazone derivatives are of special importance because of their versatile biological and pharmacological activities. Thiosemicarbazone derivatives have found application in drug development for the treatment of central nervous system disorders, of bacterial infection, as well as analgesic and antiallergic agent. Thiosemicarbazones are potent intermediates for the synthesis of pharmaceutical and bioactive materials and thus, they are used extensively in the field of medicinal chemistry. Moreover, thiosemicarbazones have found their way into almost every branch of chemistry; commercially they are used as dyes, photographic films, plastic and in textile industry.

Over the years, thiosemicarbazone derivatives have demonstrated wide range of biological activity viz. antimicrobial[52-57], antitumor[58-59], sodium channel blocker[60], anticancer[61,62], antitubercular[63], antiviral[64], as well as other industrially important activities, including anticorrosion[65] and antifouling[66] effects.

CHAPTER-II

It describe the chemistry of the reactions involved, which comprises Thiohydantoin, Styryl, Thiazolidinone, Quinazoline, Thiourea, Urea, Semicarbazide and Thiosemicarbazide.

CHAPTER-III SCHEMATIC REPRESENTATION

CHAPTER-IV EXPERIMENTAL WORK AND ANALYSIS

The experimental procedure and schematic representation of the synthesized compounds are divided into twelve series.

SERIES-1:

- **1,3-Bis[(hetero aryl)ethyl]-2-thioxoimidazolidin-4-one**

Title compounds were synthesized by the cyclisation of bis heteroaryl-ethyl thiourea with chloroacetic acid.

The required bis heteroaryl ethyl thioureas have been synthesized by the condensation of heteroaryl ethyl amines with potassium thiocynate in xylene.

SERIES-2:

- **5-(Arylidin/heteroarylidin)-1,3-bis[2-pyridin-2-yl)ethyl]-2-thioxoimidazolidin-4-one**

Title compounds were synthesized by the condensation of 1,3-bis[2-(pyridin-2-yl)ethyl]-2-thioxoimidazolidin-4-one with various substituted aryl and heteroaryl aldehydes.

The required 1,3-bis[2-(pyridin-2-yl)ethyl]-2-thioxoimidazolidin-4-one was synthesized by the cyclization of 1,3-bi[2-(pyridin-2-yl)ethyl] thiourea with chloroacetic acid.

The required 1,3-bis[2-(pyridin-2-yl)ethyl]-2-thioxoimidazolidin-4-one has been synthesized by the condensation of 2-(pyridin-2-yl)ethan-1-amine with potassium thiocynate in xylene.

SERIES-3:

- **5-(Arylidin/heteroarylidin)-1,3-bis(furan-2-yl)ethyl-2-thioxoimidazolidin-4-one**

Title compounds were synthesized by the condensation of 1,3-bis(furan-2-yl)ethyl-2-thioxoimidazolidin-4-one with various substituted aryl and heteroaryl aldehydes.

The required 1,3-bis[2-(furan-2-yl)ethyl]-2-thioxoimidazolidin-4-ones have been synthesized by the cyclisation of 1,3-bis[2-(furan-2-yl)ethyl] thiourea with chloroacetic acid.

The required 1,3-bis[2-(furan-2-yl)ethyl]-2-thioxoimidazolidin-4-ones have been synthesized by the condensation of 2-(furan-2-yl)ethan-1-amine with potassium thiocynate in xylene.

SERIES-4:

- **2-(Arylidin/heteroarylidin)-3-(pyridin-2-yl)-ethyl thiazolidin -4-one**

Title compounds were prepared by the cyclisation of substituted imines with thioglycolic acid.

The required imines have been synthesized by the condensation of 2-(pyridin-2-yl)ethan-1-amine with various substituted aryl and heteroaryl aldehydes.

SERIES-5:

- **5-(3-Bromobenzylidine)-2-(substituted aryl/heteroaryl)-3-(2-(pyridin-2-yl)ethyl)thiazolidin-4-one**

Title compounds were synthesized by the condensation of various substituted thiazolidinones with 3-bromo benzaldehyde.

The required thiazolidinones have been synthesized by the condensation of 2-(pyridin-2-yl)ethan-1-amine with various substituted aryl and heteroaryl aldehydes followed by cyclization with thioglycolic acid.

SERIES-6:

- **5-(3-Bromobenzylidine)-3-[2-(5-methoxy-1H-indol-3-yl)ethyl)-2-(aryl/ heteroaryl)-thiazolidin-4-one**

Title compounds were prepared by the condensation of various substituted thiazolidinones with 3-bromo benzaldehyde.

The required thiazolidinones have been synthesized by the condensation of 2-(5-methoxy-1H-indol-3-yl)ethan-1-amine (Tryptamine) with various substituted aryl/heteroaryl aldehydes followed by cyclisation with thioglycolic acid.

SERIES-7:

- **1-[2-{ Heteroaryl)ethyl}-3-(2-methyl quinazolin-4-yl)urea**

Title compounds were synthesized by the condensation of 4-amino quinazoline and various substituted heteroaryl ethyl isocyanates.

The required 4-amino quinazoline has been synthesized by the cyclisation of anthranilic acid with DMF, acetic anhydride and ammonium acetate followed by condensation with phosphorus oxychloride and liquid ammonia.

The required various substituted heteroaryl ethyl isocynates has been prepared by the condensation between various substituted heteroaryl ethyl amines and trichloromethyl chloroformate in toluene.

SERIES-8:

- **1-[2-{ Heteroaryl)ethyl}-3-(2-methyl quinazolin-4-yl) thiourea**

Title compounds were synthesized by the condensation of 4-amino quinazoline and various substituted heteroaryl ethyl isothiocyanates.

The required 4-amino quinazoline has been synthesized by the cyclisation of anthranilic acid with DMF, acetic anhydride and ammonium acetate followed by condensation with phosphorus oxychloride and liquid ammonia.

The required various substituted heteroaryl ethyl isothiocyanates has been prepared by the condensation between various substituted heteroaryl ethyl amines and thiophosgene in anhydrous THF.

SERIES-9:

- **2-(2-Methyl quinazolin-4-yl)-N-[2-(heteroaryl)ethyl] hydrazine-1-carboxamide**

Title compounds were synthesized by the condensation of 4-hydrazino quinazoline with various substituted heteroaryl ethyl isocyanates.

The required 4-hydrazino quinazoline has been synthesized by the cyclisation of anthranilic acid with DMF, acetic anhydride and ammonium acetate followed by condensation with phosphorus oxychloride and hydrazine hydrate.

The required various substituted heteroaryl ethyl isocyanates has been prepared by the condensation between various substituted heteroaryl ethyl amines and trichloromethyl chloroformate in toluene.

SERIES-10:

- **2-(2-Methyl quinazolin-4-yl)-N-[2-(heteroaryl)ethyl] hydrazin-1-carbothioamide**

Title compounds were synthesized by the condensation of 4-hydrazino quinazoline with various substituted heteroaryl ethyl isothiocyanates.

The required 4-hydrazino quinazoline has been synthesized by the cyclization of anthranilic acid with DMF, acetic anhydride and ammonium acetate followed by condensation with phosphorus oxychloride and hydrazine hydrate.

The required various substituted heteroaryl ethyl isothiocyanates have been prepared by the condensation between various substituted heteroaryl ethyl amines and thiophosgene in anhydrous THF.

SERIES-11:

- **1-[4-Cyclopropyl-{(2-isonicotinoyl hydrazono)methyl phenyl}-3-[heteroaryl]ethyl urea**

Title compounds were synthesized by the condensation of N'-[{4-(aminophenyl)cyclopropyl}methylene]isonicotinohydrazide with various substituted heteroaryl ethyl isocyanates.

The required N'-[{4-(aminophenyl)cyclopropyl}-methyliso] nicotino- hydrazide has been synthesized by the reaction between 4-[(chlorophenyl) cyclopropyl]methanone and isonicotinohydrazide followed by condensation with liquid ammonia.

The required isonicotinohydrazide has been prepared by reaction between isonicotinic acid and thionyl chloride followed by condensation with hydrazine hydrate.

The required various substituted heteroaryl ethyl isocynates has been prepared by the condensation between various substituted heteroaryl ethyl amines and trichloromethyl chloroformate in toluene.

SERIES-12:

- **1-[4-Cyclopropyl-{(2-isonicotinoyl hydrazono)methyl phenyl}-3-[heteroaryl]ethyl thiourea**

Title compounds were synthesized by the condensation of N'-[{4-(aminophenyl)cyclopropyl}methylene]isonicotinohydrazide with various substituted heteroaryl ethyl isothiocyanates.

The required N'-[{4-(aminophenyl) cyclopropyl}-methylisonicotino-hydrazide has been synthesized by the reaction between 4-[(chlorophenyl) cyclopropyl]methanone and isonicotinohydrazide followed by condensation with liquid ammonia.

The required isonicotinohydrazide has been prepared by reaction between isonicotinic acid and thionyl chloride followed by condensation with hydrazine hydrate.

The required various substituted heteroaryl ethyl isothiocynates has been prepared by the condensation between various substituted heteroaryl ethyl amines and thiophosgene in anhydrous THF.

ANALYSIS:

Structures of the novel synthesized compounds were established with the help of Infra Red Spectra (recorded with FT Shimadzu spectrophotometer using KBr pallets) and Nuclear Magnetic Resonance Spectra (recorded with Bruker Avance-II 400 MHz spectrophotometer).

CHAPTER – V BIOLOGICAL RESULTS AND DISCUSSION

It accommodates the biological screening of the compounds synthesized. All the novel synthesized compounds have been evaluated for their antimicrobial potential against a panel of micro organisms. Compounds were submitted for anti-HIV screening against HIV-I and HIV III (Rod) activity. SAR's have been discussed for each series.

CHAPTER – VI CONCLUSION

Some of the novel synthesized compounds were found active, moderately active and inactive against strains studied. Anti-HIV screening results are yet to come.

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